UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/550,720	06/13/2006	Vijayakumar Ramiya	0032.01 2/PCT-US	5503

25871 7590 03/02/2009

SWANSON & BRATSCHUN, L.L.C.
8210 SOUTHPARK TERRACE
LITTLETON, CO 80120

EXAMINER	
AFREMOVA, VERA	
ART UNIT	PAPER NUMBER
1657	

NOTIFICATION DATE	DELIVERY MODE
03/02/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

efspatents@sbiplaw.com

Office Action Summary	Application No.	Applicant(s)	
	10/550,720	RAMIYA, VIJAYAKUMAR	
	Examiner	Art Unit	
	Vera Afremova	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2008*.

2a)☐ This action is FINAL. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *12-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/06/2006; 04/13/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of the Group I, clams 1-12, in the reply filed on 12/01/2008 is acknowledged.

Claims 12-25 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected invention(s), there being no allowable generic or linking claim. Election was made without traverse in the reply filed on 12/01/2008.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-11 are rejected under 35 U.S.C. 102(a) as being anticipated by WO 02/079457 in the light of evidence by ATCC Catalogue.

Claims are directed to a method of trans-differentiating mammalian non-pancreatic stem cells to enter the pancreatic differentiation pathway wherein the method comprises culturing mammalian non-pancreatic stem cells under conditions that permit expression of pancreatic differentiation markers or in a culture medium comprising factors GLP-1, HGF and nicotinamide. Some claims are further drawn to mammalian cells being human and to the non-pancreatic stem cells being mesenchymal stem cells characterized by markers CD105+, CD166+, CD29+, CD44+. Some claims are further drawn to the pancreatic differentiation markers being

Pdx-1, Isl-1, Pax-4, Pax-6, Glut-2, glucagon, somatostatin, insulin and pancreatic peptide. Some claims are further drawn to the medium comprising DMEM, glucose, pyruvate, BSA, 2-mercaptoethanol, ITS and antibiotics. Some claims are further drawn to the use of particular concentrations such as 100 nM of GLP, 20 ng/L HGF and 10 nM nicotinamide. Some claims are further drawn to stimulation of insulin production with glucose.

WO 02/079457 discloses a method of trans-differentiating human non-pancreatic stem cells such as mesenchymal stem cells and hematopoietic stem cells to enter the pancreatic differentiation pathway by culturing bone marrow derived MSCs under appropriate conditions (page 7; page 13; page 16, lines 9-16) such as in a culture medium comprising factors GLP-1, HGF and nicotinamide and other basic medium components including DMEM, high glucose, pyruvate, BSA, 2- mercaptoethanol, ITS and antibiotics (pages 16-17 at see tables 1A and 1B). The cited document teaches that the trans-differentiation of bone marrow derived stem cells results in expression of the pancreatic markers including Pdx-1, Isl-1, Pax-4, Pax-6, Glut-2, glucagon and insulin (page 7 and page 19). The cited document teaches particular concentrations such as 10 nM of GLP and 20 ng/L HGF. The standard basic DMEM medium contains about 4 mg/L of nicotinamide and, thus, provides for at least 10 nM nicotinamide. The trans-differentiated bone marrow derived stem cells express insulin and, thus, they are reasonably expected to produce insulin when stimulated with glucose upon further culturing within the meaning of the claimed invention. The cited document teaches that the MSCs are CD105+, CD166+, CD29+, CD44+ (page 7, lines 27). Thus, the claimed invention is anticipated by the cited document.

Claims 1-5, 10 and 11 are rejected under 35 U.S.C. 102(a) as being anticipated by Yang et al. (IDS reference; PNAS, June 2002, 99 (2): 8078-8083).

Claims are directed to a method of trans-differentiating mammalian non-pancreatic stem cells to enter the pancreatic differentiation pathway wherein the method comprises culturing mammalian non-pancreatic stem cells under conditions that permit expression of pancreatic differentiation markers or in a culture medium comprising at least one factor such nicotinamide. Some claims are further drawn to the pancreatic differentiation markers being Pdx-1, Isl-1, Pax-4, Pax-6, Glut-2, glucagon, somatostatin, insulin and pancreatic peptide. Some claims are further drawn to the medium comprising at least some components such as DMEM, high glucose, pyruvate, and antibiotics. Some claims are further drawn to the use of particular concentrations such as 10 nM nicotinamide. Some claims are further drawn to stimulation of insulin production with glucose.

Yang et al. discloses (entire document) a method of trans-differentiating mammalian non-pancreatic stem cells such as hepatic oval cells to enter the pancreatic differentiation pathway wherein the method comprises culturing the hepatic oval cells under conditions that permit expression of pancreatic differentiation markers or in a culture medium comprising at least one factor such nicotinamide. The pancreatic differentiation markers are Pdx-1, Isl-1, Pax-4, Pax-6, Glut-2, glucagon, somatostatin, insulin and pancreatic peptide (abstract). The medium comprises DMEM, high glucose, FSB as well as other DMEM components such as pyruvate and antibiotics (page 8078 at material and methods). Yang et al. explicitly teaches the use of particular concentrations such as 10 nM nicotinamide for trans-differentiating mammalian non-

pancreatic stem cells such as hepatic oval cells into pancreatic cells or insulin producing cells (page 8081, column 2). Thus, the claimed invention is anticipated by the cited document.

Claims 1, 4, 5, 10 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 01/11011.

Claims are directed to a method of trans-differentiating mammalian non-pancreatic stem cells to enter the pancreatic differentiation pathway wherein the method comprises culturing mammalian non-pancreatic stem cells under conditions that permit expression of pancreatic differentiation markers or in a culture medium comprising at least one factor such as HGF. nicotinamide. Some claims are further drawn to the medium comprising DMEM, glucose, pyruvate, BSA, ITS and antibiotics. Some claims are further drawn to the use of particular concentrations such as 20 ng/L HGF.

WO 01/11011 discloses a method of trans-differentiating mammalian non-pancreatic stem cells such as human multipotent adult stem cell MASCs to enter the pancreatic differentiation pathway wherein the method comprises culturing MASCs under conditions that permit expression of pancreatic differentiation markers or in a culture medium comprising at least one factor such as HGF. WO 01/11011 teaches the use of the medium comprising DMEM, glucose, pyruvate, BSA, ITS and antibiotics and the use of 0.5-1000 mg/ml HGF for expression of markers of pancreatic cells (entire document page 84, lines 19-31). Thus, the claimed invention is anticipated by the cited document.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 02/079457, WO 01/11011, Yang et al. (IDS reference; PNAS, June 2002, 99 (2): 8078-8083), Petersen et al. (IDS reference; Science, 1999, vol. 284, pages 1168-1170) and ATCC Catalogue.

The cited documents WO 02/079457, WO 01/11011 and Yang et al disclose methods of trans-differentiating various non-pancreatic stem cells to enter the pancreatic differentiation pathway by culturing the stem cells under appropriate conditions. The non-pancreatic stem cells include human multipotent cells (WO 01/11011), bone marrow derived mesenchymal stem cells that are CD105+, CD166+, CD29+, CD44+ (WO 02/079457) and hepatic oval cells (Yang et al). The cited documents WO 02/079457, WO 01/11011 and Yang et al teach the appropriate conditions of trans-differentiation of the stem cells into pancreatic cells wherein the conditions include the use of at least some components such as DMEM, glucose, pyruvate, BSA, 2-mercaptoethanol, ITS and antibiotics and at least some factors such as GLP-1, HGF and nicotinamide. The concentration ranges of GLP-1, HGF and nicotinamide as disclosed by the cited documents include the presently claimed concentrations as explained above. In addition, ATCC Catalogue is relied upon to demonstrate that DMEM medium used in the methods of the cited reference inherently provides for nicotinamide. The cited references by Yang et al. explicitly teaches the use of particular concentrations such as 10 nM nicotinamide for trans-differentiating mammalian non-pancreatic stem cells into pancreatic cells or insulin producing cells (page 8081, column 2).

Thus, the cited references WO 02/079457, WO 01/11011 and Yang et al combined teach and/or suggest all claimed limitations. Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to combine the teaching of the cited references with a reasonable expectation of success in producing pancreatic cells from non-pancreatic stem cells as encompassed by the presently claimed method because one of skill in the art is free to select components available in the prior art. Thus, the claimed invention as a whole was clearly *prima facie* obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

In addition, the cited reference by Petersen et al. teaches that bone marrow cell population contains oval cells that are hepatic stem cells (see entire document including abstract). Yang et al. demonstrates that the oval cells or the hepatic stem cells are stimulated to produce insulin by culturing in a medium with high glucose or by switching from media with low glucose to media with higher glucose concentration (see entire document including abstract).

Thus, the claimed invention would have been obvious to one having ordinary skill in the art at the time the claimed invention was made because the prior art teaches and suggests that bone marrow stem cells enter the pancreatic differentiation pathway under appropriate conditions and because non-pancreatic stem cells including bone marrow-derived oval cells are stimulate by glucose to produce endocrine hormone including insulin.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection

is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-11are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 7,202,080 in view of ATCC Catalogue.

Although the conflicting claims are not identical, they are not patentably distinct from each other because they are directed to similar methods of trans-differentiating mammalian non-pancreatic stem cells to enter the pancreatic differentiation pathway wherein the methods comprise same active steps of culturing mammalian non-pancreatic stem cells under conditions that permit expression of pancreatic differentiation markers or in a culture medium comprising factors GLP-1, HGF and nicotinamide. In both patented and pending claims the pancreatic differentiation markers include Pdx-1, Isl-1, Pax-4, Pax-6, Glut-2, glucagon and insulin. The base medium in the methods of issued patent and pending claims comprise DMEM, glucose, pyruvate, BSA, 2- mercaptoethanol, ITS and antibiotics.

The patented claims are narrower and limited to non-pancreatic stem cells such as mesenchymal and hematopoietic stem cells. However, some of the pending claims are also

limited to mesenchymal stem cells characterized by the same markers CD105+, CD166+, CD29+, CD44+.

The culture medium in the methods of issued patent and pending claims comprise DMEM, glucose, pyruvate, BSA, 2- mercaptoethanol, ITS and antibiotics. Although the issued claims do not explicitly recite the use of nicotinamide. The presence of nicotinamide in DMEM is evidenced by ATCC Catalogue, for example: page 516.

Accordingly, the claimed processes in the issued patent and in the present application are obvious variants. Therefore, the inventions as claimed are co-extensive.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (571) 272-0914. The examiner can normally be reached from Monday to Friday from 9.30 am to 6.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber, can be reached at (571) 272-0925.

The fax phone number for the TC 1600 where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Technology center 1600, telephone number is (571) 272-1600.

Vera Afremova

February 23, 2009

/Vera Afremova/

Primary Examiner, Art Unit 1657